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CURRENT OPINION

Of fads, fashion, surrogate endpoints and dual RAS blockade

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Background Dual renin–angiotensin system (RAS) blockade, mostly by combining an angiotensin converting enzyme (ACE) inhibitor with an angiotensin receptor blocker (ARB), is increasingly used in patients with hypertension and diabetes and/or proteinuria and in those with resistant heart failure. However, in the zest of achieving greater nephroprotection and cardioprotection, even patients with uncomplicated essential hypertension are not uncommonly treated with dual RAS blockade.

Evidence In 2003 the COOPERATE trial, seemed to confirm that dual RAS blockade was beneficial and that proteinuria reduction was synonymous with nephroprotection. This study had to be withdrawn recently attesting to the suspicion that the data looked to good to be true. Moreover, the large prospective ONTARGET data argue against a nephroprotective effect of dual RAS blockade and together with renal findings from ACCOMPLISH, cast doubt on albuminuria/proteinuria being a reliable surrogate endpoint for renal outcome. Although in heart failure, dual RAS blockade had some benefit without reducing mortality, there remains a distinct safety issue with regard to hyperkalemia and elevated creatinine. Neither in ischaemic heart disease nor in left ventricular hypertrophy had dual RAS blockade any benefits when compared with single RAS blockade. Of note, the combination of an ACE inhibitor with an ARB was recently shown to reduce the risk of dementia. All dual RAS blockade may be created equal and the combination of valsartan with aliskiren, a direct renin inhibitor will be evaluated in diabetic patients in the prospective, randomized ALTITUDE study.

Conclusions For the time being, given the adverse effects and lack of consistent survival benefits, the use of dual RAS blockade should be avoided unless ironclad data emerge to the contrary.

Keywords RAS blockers • Hypertension • Heart failure • LVH • Coronary heart disease • DRI • Aldosterone blockers

Background

The concept of dual renin–angiotensin system (RAS) blockade originated from the elegant animal model created by Menard *et al.*[1] purporting to show a 'synergistic' effect between angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). It was hoped that combining the two drug classes would be a way to avoid the escape phenomenon[2] occurring because of incomplete blockade of the RAS with monotherapy of either an ACE inhibitor or an ARB. Dual RAS blockade was promptly accepted primarily by nephrologists while it remained less poplar among practicing physicians and cardiologists in spite of the guidelines and evidence derived from some studies. The concept seemed so logical and appealing that changes in surrogate endpoints such as blood pressure, proteinuria, endothelial dysfunctions became accepted as a free pass for this combination having cardioprotective and nephroprotective effects. Despite a lack of solid evidence on safety and efficacy dual RAS blockade found entrance into several sets of recent guidelines.

Current use of dual RAS blockade

In a meta-analysis of 49 studies with more than 6000 patients, Kunz *et al.*[3] found 'encouraging' evidence that dual RAS blockade reduced proteinuria by 20–25% more than either drug alone. Thus, dual RAS blockade is most commonly used in patients with hypertension and diabetes and/or proteinuria and also to a lesser extent in those with resistant heart failure. However, even

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patients with uncomplicated essential hypertension were not entirely able to escape this fashionable trend. In the USA more than 200 000 patients are currently treated with dual RAS blockade.[4] Among these, the combination of an ARB and an ACE inhibitor is by far the most common (70%) though other combinations such as two ACE inhibitors (15%), two ARBs (5%) and ACE inhibitors or ARBs in combination with a direct renin inhibitor (8%) are used as well. To us, the raison d'être of some of these combinations is not entirely evident. Clearly, such a prescribing pattern reflects a distinct need for education.

The COOPERATE study

In 2003 a randomized control trial of 336 patients with non-diabetic renal disease (COOPERATE) showed that dual RAS inhibition with trandolapril and losartan reduced the risk of primary endpoint (time to doubling of serum creatinine or end stage renal disease) by a stunning 60% compared with monotherapy.[5] Not surprisingly, the COOPERATE study brought oil to the fire of dual RAS blockade and became one of the Lancet's most widely quoted papers.[6] It was argued that 'differences in renal protection are probably due to the much larger anti-proteinuric effect of dual blockade'[7] and 'one should not only apply dual RAS blockade as fixed dose titration for proteinuria—but specifically pursue the lowest level of proteinuria by individual dose titration. . . .'[7] After the seemingly ironclad evidence put forward by the COOPERATE trial, many physicians accepted the dictum that proteinuria reduction was synonymous with nephroprotection.

Surrogate endpoints terminology and surrogate endpoint failure

The FDA has defined a surrogate endpoint, or 'marker,' as 'a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy'.[8] This definition implies that the surrogate endpoint is not of any value to the patient *per se*.[9] Unfortunately, surrogate endpoints such as microalbuminuria, left ventricular hypertrophy (LVH) and endothelial function have become synonymous for most physicians with outcome. Indeed, even reputable journals seem to be careless about surrogate endpoint terminology. Based on the fact that the urinary albumin to creatinine ratio was reduced in patients who received aliskiren as compared with those receiving placebo, Parving *et al.*,[10] in the AVOID study, concluded that aliskiren may have 'renoprotective' effects that are independent of its blood pressure. In contrast, Mauer *et al.*[11] documented in the same journal that the 5 year cumulative incidence of microalbuminuria was almost three times higher with losartan than with placebo ($P < 0.01$ by the log-rank test). To be consistent with regard to this surrogate endpoint terminology, should we now conclude that indeed losartan has 'renodestructive' properties? Pharmaceutical companies and investigators alike seem to have a tendency to use euphemistic terminology when dealing with the soft science of surrogate endpoints.

ONTARGET, COOPERATE, ACCOMPLISH

The halo of dual RAS inhibition was finally shattered by the findings of the large ONTARGET study.[12] Similarly to previous findings, albuminuria was reduced with the combination of telmisartan and ramipril compared with monotherapy. However, since there was significantly more doubling of creatinine and dialysis in the combination arm (despite less albuminuria), ONTARGET clearly argued against a nephroprotective effect of dual RAS inhibition and also casts doubt on the contention of albuminuria being a surrogate endpoint for renal outcome. At the same time a 'letter of concern' by Kunz *et al.*[13] found a number of serious inconsistencies in the COOPERATE study thereby casting some doubt on the veracity of these data. Further attesting to the unreliability of albuminuria as a surrogate end point are recent findings in the ACCOMPLISH study.[14] Although albuminuria was reduced in both treatment groups, the overall reduction was greater in the benazepril plus hydrochlorothiazide group than in the benazepril plus amlodipine group despite the fact that the amlodipine combination slowed progression of nephropathy to a greater extent.

Heart failure

Benefits of dual RAS blockade were not only thought to be present in diabetic hypertensive patients but also in patients with New York Heart Association function Class 3 or 4 of heart failure. In CHARM, the addition of candesartan reduced all components of the primary outcome, total number hospital admissions for heart failure, but not all cause mortality.[15] Of note, the study was not powered to show a mortality reduction. With the addition of an ARB a slight reduction in mortality of 11% ($P = 0.086$) in heart failure was only seen in the CHARM/added (Candesartan in Heart Failure—Added Trial) study[16] and not in the CHARM/alternative (Candesartan in Heart Failure—Alternative Trial) study[17] or the ValHeft (Valsartan Heart Failure Trial) study.[18] In ValHeft, the bulk of the benefits occurred in ACE inhibitor intolerant patients. In the few patients who received valsartan and an ACE inhibitor the morbidity benefits were significant only in those on a low ACEi dose.[19]

In the combined study of Young *et al.*[20] candesartan, when added in a prespecified subgroup with a low ejection fraction (<40%) resulted, in almost twice as many patients, in a small but significant all-cause mortality reduction with a hazard ratio of 0.88 (CI: 0.79–0.98). Little surprise that patients who were not already receiving an ACEi responded to the addition of an ARB. The mortality benefits of the candesartan addition in the combined analysis were therefore mainly driven by the patients who were ACEi intolerant (and therefore only received an ARB and not dual RAS blockade).

Despite all of these caveats, the evidence seemed to be sufficient for recommending dual RAS blockade in guidelines for heart failure.[21,22] However, to our way of thinking, the benefits of dual RAS blockade in heart failure may not be quite as robust as some would like them to be.

A major concern in heart failure is the safety issue. In CHARM hyperkalemia was almost five times more common, and elevated creatinine occurred twice as much with dual RAS blockade than with monotherapy. A recent meta-analysis in over 18 000 patients with left ventricular dysfunction showed a significantly increased risk of adverse events leading to the discontinuation of dual RAS blockade compared with monotherapy.[23] Thus, hypotension, worsening of renal function and hyperkalemia were more common with combination therapy than with ACE inhibitor therapy alone. Similarly, Kuenzli *et al.*[24] found no benefit of dual RAS blockade compared with monotherapy but more hyperkalemia, renal dysfunction and hypotension in an analysis of RESOLVD,[25] Val Heft,[18] CHARM-ADDED[16] and VALIANT.[26] Thus, given the adverse effects and lack of consistent survival benefits, the routine addition of an ARB to ACE inhibitor therapy in heart failure patients should be reserved for selected patients who remain symptomatic on monotherapy. Clearly, dual RAS blockade requires strict monitoring of renal function and potassium and monitoring symptoms and signs of hypotension.

Left ventricular hypertrophy

In a small experimental study, dual RAS inhibition improved ventricular lusitropy without affecting cardiac fibrosis.[27] Similarly, Grandi *et al.*[28] reported a 'beneficial' effect of dual RAS blockade on concentric (LVH) in hypertensive patients in a randomized controlled study. However, in ONTARGET, the prevalence of (LVH) was very similar to dual RAS blockade as with monotherapy despite the fact that the blood pressure was lower throughout the study with dual RAS blockade.[29] In ALLAY the reduction in the LV mass with the combination of losartan plus aliskiren was not significantly different from that with losartan monotherapy, independent of blood pressure lowering.[30] Thus in neither ONTARGET nor ALLAY did the surrogate endpoint (LVH) move in the expected direction with dual RAS blockade. This lack of incremental LVH reduction argues therefore, to some extent, against a cardioprotective effect of dual RAS inhibition. However, as the LIFE study[31] taught us, neither is LVH an infallible surrogate endpoint: although a significantly greater reduction in LVH occurred in the losartan arm than in the atenolol arm, the rate of myocardial infarction (MI) if anything remained higher and the rate of heart failure was not reduced with losartan.[32,33]

Ischaemic heart disease

Recently, Baker *et al.*[34] assessed the risk–benefit ratio of RAS and dual RAS inhibition in patients with stable ischaemic heart disease. Angiotensin converting enzyme inhibitor therapy reduced the relative risk for total mortality and MI but increased the risk for syncope by 24% compared with placebo. The authors contrast this with the ONTARGET study in which dual RAS blockade neither reduced total mortality nor MI but significantly increased the risk of hypotension and syncope compared with ACE inhibitor therapy alone. Their conclusion was that dual RAS blockade seemed no better than ACE inhibitor therapy alone and increased harm.[34]

Cognitive dysfunction and dementia

Of interest is the recent study by Li *et al.*[35] in 819 491 predominantly male patients aged 65 or more with cardiovascular disease from the administrative database of the US Veteran Affairs. In this prospective cohort analysis, dual RAS blockade compared with ACEi monotherapy was associated with a reduced risk of incident dementia (0.54, 0.51–0.57) and admission to a nursing home (0.33, 0.22–0.49). ARBs exhibited a dose–response as well as additive effects in combination with ACEi. Thus, dual RAS blockade may offer some health benefits to those with cognitive decline. These data are provocative and should be considered as hypothesis generating only—a hypothesis important enough though to be thoroughly and expeditiously explored.

Not all dual RAS blockade is created equal

Direct renin inhibitors

In the past year another class of RAS blocker has become available, represented by aliskiren, a direct renin inhibitor.[36] Thus, dual RAS blockade can now be achieved by combining an ACE inhibitor with an ARB, an ACE inhibitor with a direct renin inhibitor, or an ARB with a direct renin inhibitor. Since ARBs and ACE inhibitors both increase plasma renin activity and only partially block the RAS, the argument has been put forward that the addition of a drug class such as a direct renin inhibitor, which decreases plasma renin activity, has the potential to be more beneficial than blockade with either an ACE inhibitor or an ARB alone.[37] In theory, this is an attractive concept and certainly deserves to be scrutinized in outcome studies. Indeed, in a thorough double-blind study of 1797 hypertensive patients, a further fall in BP of 4.4–2.5 mmHg was seen when aliskiren was added to patients who were on the maximal dose of valsartan.[38] However, at least in patients having suffered an acute MI, the addition of aliskiren to either an ACEi or an ARB did not further protect against ventricular remodeling in the prospective randomized ASPIRE trial.[39] Of note, in ASPIRE there was significantly more hypotension and hyperkalemia with dual RAS blockade than with the ACEi or the ARB alone. The combination of valsartan with aliskiren will be thoroughly tested in diabetic patients in the ALTITUDE study. Other randomized trials are currently investigating the benefit of combining aliskiren with ARBs or ACE inhibitors such as ATMOSPHERE and ASTRONAUT in chronic and acute heart failure, respectively.

Aldosterone blockers

The addition of an aldosterone blocker, either spironolactone or eplerenone, to an ACE inhibitor or an ARB has been examined in a number of trials. Dual blockade with an aldosterone blocker decreases proteinuria[40] and LVH[41] beyond what is achieved by either component of the combinations alone. No study has compared proteinuria reduction of dual blockade with an aldosterone blocker with dual blockade of ACE inhibitor/ARB. In heart failure, however, in sharp contrast with dual RAS blockade by ARB/ACE

inhibitor, the RALES trial[42] as well as more recently, EPHESUS[43] showed that aldosterone blockers prolong survival, when added to usual care, including ACE inhibitor therapy. Worsening of renal function and hyperkalemia were also more common when combining an aldosterone blocker with ACE inhibition and close monitoring is warranted. Since close monitoring is mandatory in these patients, the level of available evidence would favour addition of an aldosterone blocker as the next step in heart failure on ACE inhibitor therapy rather than an ARB. In two recent meta-analysis, mortality was reduced by 25% ($P < 0.00001$) with the addition of aldosterone blockade[44] as opposed to no significance with dual RAS blockade.[45] Thus, the data in aggregate (and cost) seem to favour the addition of aldosterone blockade over ARBs.

Conclusion

The Lancet has now retracted the COOPERATE study thereby confirming the lingering suspicion that these findings looked too good to be true.[46] Hopefully this retraction, together with findings from studies such as ONTARGET and ACCOMPLISH together with the meta-analysis of Lakhdar *et al.*[23] will convince practicing physicians that dual RAS inhibition with an ARB and an ACE inhibitor was a fad whose time has come and gone. The sobering data evolving from studies with dual RAS blockade should remind us that surrogate endpoint failure is not uncommon and that leapfrogging from surrogate data cannot ultimately substitute for patient exposure in clinical outcome studies.

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